Supplementary Material

Appendix A

Statement regarding approvals by relevant authorities

Denmark:
According to Danish law, studies based entirely on registry data do not require approval from an ethics review board. The study was registered at the repository of the University of Southern Denmark (11.423) and data were available from the Danish Health Data Authority (FSEID00005818). Due to legal reasons, individual-level data cannot be shared by the authors.

Norway:

The study was approved by the Regional Ethical Committee B, South East Norway (ref 547020/REK sør-øst B). Due to legal reasons, individual-level data cannot be shared by the authors.

Sweden:

The study was approved by the Swedish Ethical Review Authority (no. 2020/07088–02/9). Due to legal reasons, individual-level data cannot be shared by the authors.

The Netherlands:

This study analysed de-identified data from the PHARMO Database Network; therefore, the study was exempt from ethical review and informed consent was not required. The data in this study are available from the PHARMO Database Network. As restrictions apply to the availability of these data, they are not publicly available.

Germany:

In Germany, the utilisation of health insurance data for scientific research is regulated by the Code of Social Law. All involved health insurance providers as well as the German Federal Office for Social Security and the Senator for Health, Women and Consumer Protection in Bremen as their responsible authorities approved the use of GePaRD data for this study. Informed consent for studies based on claims data is required by law unless obtaining consent appears unacceptable and would bias results, which was the case in this study. According to the Ethics Committee of the University of Bremen studies based on GePaRD are exempt from institutional review board review.

Italy:

In Italy retrospective studies based on administrative health care data require only notification to Ethical Committees. Department of Epidemiology of Lazio notified the protocol to EC on behalf of all centres. In addition, special agreements for the access and analyses of claims data are in place between each centre and respective data provider. For the region of Tuscany, the study has been included in the institutional program of ARS Toscana. Due to legal reasons, individual-level data cannot be shared by the authors.

Supplementary Table 1. An overview of main-, supplementary- and sensitivity analyses of the association between use of brodalumab and suicide attempts, serious infections, MACE and cancer. Each bullet under *supplementary and sensitivity analyses* describes how the analysis differs from the main analysis.

	Case-time-control design	**Active-comparator cohort design**
Suicide attempts		
Main analyses	Event/index date: First occurrence of the composite of fatal and non-fatal suicide attempts during eligibility period for cases and corresponding date for controls Study population: Restricted to brodalumab users without a history of psychiatric disease, suicide attempt, use of anti-depressants or use of lithium Exposure: Brodalumab Time intervals: 4 months Method of dispensing duration estimation: WTD, 95th percentile, log-normal backward recurrence distribution Adjustment for time varying activity No comparison to contrasting use	Cohort entry: Start of incident treatment episode of drug of interest Study population: Restricted to individuals without a history of psychiatric disease, suicide attempt, use of anti-depressants or use of lithium Outcome: First occurrence of the composite of fatal and non-fatal suicide attempts during eligibility period Exposure: Brodalumab vs. TNF-alpha inhibitors, IL-12 and IL-23, other inhibitors of IL-17(substance group level) Confounder adjustment: 1:4 propensity score matching with replacement Method of dispensing duration estimation: WTD, 95th percentile, log-normal backward recurrence distribution
Supplementary and sensitivity analyses (Differs from main analysis by)	1. Subgroup analysis with comparison to contrasting use 2. Study population: No restriction by psychiatric history 3. Time intervals: 2 months 4. Time intervals: 6 months 5. No adjustment for time varying activity 6. Outcome: Death by suicide 7. Outcome: First suicide attempt during eligibility period	1. Study population: No restriction by psychiatric history 2. Cohort entry: Not restricted to incident treatment episode 3. Confounder adjustment: IPTW 4. Exposure: Brodalumab vs. ustekinumab, etanercept, adalimumab, secukinumab, and ixekizumab (substance level) 5. Outcome: Death by suicide 6. Outcome: First suicide attempt during eligibility period

	8. Method of dispensing duration estimation: WTD, 90th percentile, log-normal backward recurrence distribution 9. Method of dispensing duration estimation: WTD, 95th percentile, Weibull distribution	7. Method of dispensing duration estimation: WTD, 90th percentile, log-normal backward recurrence distribution 8. Method of dispensing duration estimation: WTD, 95th percentile, Weibull distribution
Serious infections		
Main analyses	Event/index date: First occurrence of a serious infection i.e., the composite of acute serious infections and chronic infections, during the eligibility period Study population: Restricted to brodalumab users without a history of chronic infections Exposure: brodalumab Time intervals: 4 months Method of dispensing duration estimation: WTD, 95th percentile, log-normal backward recurrence distribution Adjustment for time varying activity No comparison to contrasting use	Cohort entry: Start of incident treatment episode of drug of interest Study population: Restricted to individuals without a history of chronic infections Outcome: first occurrence of a serious infection i.e., the composite of acute serious infections and chronic infections, during the eligibility period Exposure: Brodalumab vs. TNF-alpha inhibitors, IL-12 and IL-23, other inhibitors of IL-17(substance group level) Confounder adjustment: 1:4 propensity score matching with replacement Method of dispensing duration estimation: WTD, 95th percentile, log-normal backward recurrence distribution
Supplementary and sensitivity analyses (Differs from main analysis by)	1. Subgroup analysis with comparison to contrasting use 2. Study population: Restricted to brodalumab users without a history of either acute serious infection or chronic infections 3. Time intervals: 2 months 4. Time intervals: 6 months 5. No adjustment for time varying activity 6. Outcome: First acute serious infection during the eligibility period	1. Study population: Restricted to individuals without a history of either acute serious infection or chronic infections 2. Cohort entry: Not restricted to incident treatment episode 3. Confounder adjustment: IPTW 4. Exposure: Brodalumab vs. ustekinumab, etanercept, adalimumab, secukinumab, and ixekizumab (substance level) 5. Outcome: First acute serious infection during the eligibility period

	7. Method of dispensing duration estimation: WTD, 90th percentile, log-normal backward recurrence distribution 8. Method of dispensing duration estimation: WTD, 95th percentile, Weibull distribution	6. Method of dispensing duration estimation: WTD, 90th percentile, log-normal backward recurrence distribution 7. Method of dispensing duration estimation: WTD, 95th percentile, Weibull distribution
MACE		
Main analyses	Event/index date: First occurrence of MACE during eligibility period Study population: All brodalumab users. No restriction by outcome Exposure: Brodalumab Time intervals: 4 months Method of dispensing duration estimation: WTD, 95th percentile, log-normal backward recurrence distribution Adjustment for time varying activity No comparison to contrasting use	Cohort entry: Start of incident treatment episode of drug of interest Study population: No restriction by history MACE Outcome: first occurrence of a MACE during the eligibility period Exposure: Brodalumab vs. TNF-alpha inhibitors, IL-12 and IL-23, other inhibitors of IL-17(substance group level) Confounder adjustment: 1:4 propensity score matching with replacement Method of dispensing duration estimation: WTD, 95th percentile, log-normal backward recurrence distribution
Supplementary and sensitivity analyses (Differs from main analysis by)	1. Subgroup analysis with comparison to contrasting use 2. Study population: Restricted to brodalumab users without a history of MACE, acute coronary syndrome, or transitory ischemic attack 3. Time intervals: 2 months 4. Time intervals: 6 months 5. No adjustment for time varying activity 6. Method of dispensing duration estimation: WTD, 90th percentile, log-normal backward recurrence distribution 7. Method of dispensing duration estimation: WTD, 95th percentile, Weibull distribution	1. Study population: Restricted to individuals without a history of MACE, acute coronary syndrome, or transitory ischemic attack 2. Cohort entry: Not restricted to incident treatment episode 3. Confounder adjustment: IPTW 4. Exposure: Brodalumab vs. ustekinumab, etanercept, adalimumab, secukinumab, and ixekizumab (substance level) 5. Exposure: Ever use of brodalumab vs. any active comparator 6. Cumulative use of brodalumab vs. any biologics used in the treatment of psoriasis

		7. Method of dispensing duration estimation: WTD, 90th percentile, log-normal backward recurrence distribution 8. Method of dispensing duration estimation: WTD, 95th percentile, Weibull distribution
Cancer		
Main analyses	Not applicable	Cohort entry: Start of any treatment episode but restricted to episodes that are incident or follow an incident episode within eligibility period Study population: Restricted to individuals without a history of cancer Outcome: First cancer diagnosis ever Exposure: Ever use of brodalumab vs. any active comparator Lag-time: 12 months Confounder adjustment: 1:4 propensity score matching with replacement Method of dispensing duration estimation: WTD, 95th percentile, log-normal backward recurrence distribution
Supplementary and sensitivity analyses (Differs from main analysis by)		1. Study population: No restriction by cancer history 2. Lag-time: 6 months 3. Lag-time: 24 months 4. Outcome: first cancer diagnosis ever excl. NMSC 5. Confounder adjustment: IPTW 6. Cumulative use of brodalumab vs. any biologics used in the treatment of psoriasis 7. Method of dispensing duration estimation: WTD, 90th percentile, log-normal backward recurrence distribution

	8. Method of dispensing duration estimation: WTD, 95th percentile, Weibull distribution

WTD: Waiting time distribution; IPTW: Inverse probability of treatment weighting; TNF: Tumor necrosis factor; MACE: Major adverse cardiac events; NMSC: Non-melanoma skin cancer